THE RELATIONSHIP OF FOLIC ACID DEFICIENCY TO NEUROLOGICAL AND PSYCHIATRIC DISORDERS

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The Relationship of Folic Acid Deficiency to Neurological and Psychiatric Disorders

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INTRODUCTION

It is quite well established that deficiency of vitamin B_{12} may cause neurological complications[6,9]. It is not widely accepted that deficiency of folic acid may also cause neurological complications. In fact, aggravation of the neurological complications of patients with pernicious anemia treated with folic acid has been reported and suggests that the administration of this vitamin may be harmful to the nervous system under some circumstances. However, some recent studies in epileptic and psychiatric patients have raised some interesting and unanswered questions about the role of folic acid and the significance of folic acid deficiency for nervous system function.

There is evidence from studies in epileptic patients of an association of mental illness with low folate levels in serum, red cells and CSF.[3, 14,20,21] There have been reports of improvement in mental state in epileptics with folate deficiency when treated with folate.[12,17] Several studies and case reports have suggested a relationship between folate deficiency and nervous system function in a non-epileptic population.[1,2,4,5,7.13,22] But, there is also evidence against any role for folate deficiency in the development of psychiatric and neurological complications.[10,11,15,23]

Thus, while some of the studies in epileptics and non-epileptics suggest that folic acid deficiency may be harmful to the central nervous system, the evidence is conflicting in part, and the significance of folic acid deficiency for the nervous system remains uncertain. In Brain's Diseases of the Nervous System for example, it is suggested that, "estimation of the serum folate should be carried out in cases of unexplained polyneuropathy, myelopathy and dementia, although the exact role of folate deficiency in these disorders remains to be determined." That folic acid must be important in central nervous system metabolism is suggested by the fact that the CSF folate level is normally three times that in the serum.[8]

There have been no studies of the incidence of neurological or psychiatric

disorders in patients with folic acid deficiency. In this study I hoped to learn whether there is a higher incidence of neurologic disease in patients with low serum folate levels than in those without evidence of such a deficiency.

METHOD

Subjects

The subjects were 45 in-patients at the Yale-New Haven Medical Center and at the West Haven Veterans Administration Hospital. Thirty-four of these patients were seen at Yale-New Haven and 11 were seen at the Veterans Hospital. The majority of the patients were on the general medical service. None were on the neurology service in order to limit bias as much as possible in the selection of patients for folate determination. There were 33 males (including all 11 from the Veterans Hospital) and 12 females.

The ages of the patients with low serum folic acid levels ranged from 28 to 94 with a mean age of 55.5 (SEM $\pm$ 3.5). The ages in the control group with normal folate ranged from 30 to 81 with a mean age of 56.8 (SEM $\pm$ 2.9). There were 18 males and 6 females in the low folate group and 15 males and 6 females in the control group.

There were 20 alcoholic patients, 12 of whom had low serum folic acid levels. A patient was considered alcoholic if he had biopsy proven Laennec's cirrhosis, a clinical diagnosis of cirrhosis and/or gave a history of constant alcohol consumption causing a loss of time from work or disruption of home life.

Procedure

Patients with folic acid deficiency were selected in the clinical microscopy laboratory where all serum folic acid determinations for the Yale-New Haven Hospital and West Haven Veterans Administration Hospital are performed (Dr. Barnes, Clinical Microscopy, Memorial Unit). Although serum

folic acid concentrations of <5ng/ml are considered low in this laboratory, only patients with levels < 3ng/ml (severe deficiency) were included in the deficient group in order to avoid all doubts. The observers had no prior knowledge of the physical or mental state of these patients. During the period of this study, all patients on whom a CBC was ordered had RBC indices performed. Folate levels were performed by Dr. Barnes routinely on all patients with macrocytic indices whether or not the physician in charge had requested folate values. In a minority of the cases serum folate values had been specifically requested as an index of the nutritional state of the patient (most of these were from the Veterans Hospital). As best as we could determine, in no case did the neurologic condition of the patient provide the reason for estimating serum folic acid. The basic criterion for the inclusion of patients in the control group was a serum folic acid level > 6.9ng/ml. Once the level was determined, the patient's chart was reviewed. As far as possible patients were chosen for the control group because of similar age, sex and basic disease processes as those patients with chemical evidence of folic acid deficiency, but otherwise the observers had no direct knowledge of the physical or mental state of these patients. Serum folate was determined by the Lactobacillus casei method and serum vitamin B_{12} by the Co^{57} method.

Each patient had a mental status and neurological examination. In the mental status examination attention was paid to behavior, mood, speech, thought content, memory, concentration, intelligence and orientation. Memory was evaluated by questions about recent, remote and immediate incidents. Immediate memory was checked by a patient's ability to repeat 7 digits forward and 3 digits backward. Patients who had attended high school were asked to subtract 7 serially from 100 and others to subtract 3 serially. The patient's fund of general information was estimated by questions geared

to his educational level and interests (e.g. name of the President and his immediate predecessors, 5 large cities in the U.S.). Patients were asked to interpret proverbs (e.g. the early bird catches the worm) and similarities (e.g. how are an orange and an apple alike). Orientation was judged by the patient's ability to know who he was, where he was and the day, month and year. Mental status was not graded except normal or abnormal on the basis of the examiner's experience.

In the neurological examination special emphasis was placed on the possibility of subacute combined degeneration of the spinal cord and peripheral neuropathy. Clinical signs of injury to the posterior column tested were loss of position sense in the toes, impairment of ability to recognize vibration over the legs and loss of two point discrimination. Babinski signs were looked for as indication of degeneration of the pyramidal tracts. Pinprick sensation was tested in the hands and feet and the biceps, triceps, patellar and ankle reflexes were examined. In each case where there was even a suspicion of any abnormal findings the patient was also examined by Dr. Jonathan Pincus, Associate Professor of Neurology, or Dr. E.H. Reynolds, Visiting Assistant Professor of Neurology. Neither Dr. Pincus nor Dr. Reynolds was aware of the patient's folate level at the time of examination. For purposes of this study all abnormal sensory findings were classified together as neuropathy.

It is difficult on the basis of physical examination alone to distinguish position sense loss which occurs as a result of peripheral neuropathy from that which results from posterior column damage. It is even more difficult to assess posterior column function in the presence of mild neuropathy. Furthermore, it is not unusual in patients over 50 years of age to find minor changes in the appreciation of vibratory sensation in the lower extremities and the average age of patients in this study was about 55. For these reasons I have not attempted to distinguish posterior column loss from peripheral

neuropathy in cases where physical signs were compatible with either or both, and I regarded position sense loss as evidence of peripheral neuropathy for the purposes of this study. If position and vibration sense were severely impaired in a patient whose pinprick sensation and deep tendon reflexes were preserved, one could be more certain of posterior column damage. However, none of the patients in this study had such clear cut evidence.

In evaluating the mental status of a patient, it is sometimes difficult to distinguish reactive depression from mild dementia. Indeed, both often occur simultaneously. For the purposes of this study, we have included the 5 patients (2 with folate deficiency and 3 controls) who showed disabling apathy and depression in the category of organic brain syndrome although other tests of intellectual functioning were not greatly disordered.

RESULTS

The patients with folic acid deficiency were compared with controls (Table 1). There were 24 patients in the low folate group of whom 17 had an organic brain syndrome (OBS); 3 had cerebellar dysfunction; 14 had neuropathy; 5 demonstrated a Babinski sign and 2 were entirely normal. In the control group, there were 21 patients. Of these, 8 had an OBS; 1 had cerebellar dysfunction; 7 had neuropathy ; none demonstrated the Babinski sign and 8 were entirely normal. The difference between these groups is statistically significant in the findings of OBS ($p < .03$) and of the Babinski sign ($p < .03$). The incidence of neuropathy was also considerably higher in the folate deficient group.

To eliminate the factor of severe anemia, all patients with a hemoglobin (Hb) of less than 10 were eliminated (Table 2). There were 31 patients left, 12 with low folates and 19 with normal folates. In the low folate group, 8 had an OBS; 1 had cerebellar dysfunction; 8 had neuropathy ; 3 demonstrated the Babinski sign and only one was entirely normal. In the normal folate group,

7 had an OBS; 1 had cerebellar dysfunction; 6 had neuropathy; none demonstrated a Babinski sign and 7 were entirely normal. The incidence of the Babinski sign is significantly greater in the low folate group ($p < .025$). The incidence of other signs was also considerably higher in the low folate group; OBS (66.7%) and neuropathy (66.7%) as compared to the normal folate group where the incidence was 36.8% and 31.6% respectively, but these differences just fell short of statistical significance.

The low folate group was then divided according to Hb content into a group with Hb ≤ 10 (severe anemia) and a group with Hb > 10 (Table 3). There were 12 anemic low folate patients of whom 9 had an OBS; 2 had cerebellar dysfunction; 6 had neuropathy and 2 demonstrated a Babinski sign. In the non-anemic low folate group of 12 patients; 8 had an OBS; 1 had cerebellar dysfunction; 8 had neuropathy and 3 demonstrated a Babinski sign. In each group there was only one patient without any abnormal findings. The incidence of neurological complications is thus essentially the same in folate deficient patients whether or not they are anemic.

Alcoholic patients with low and normal serum folates were compared (Table 4). There were 12 patients in the low folate group of whom 8 had an OBS; 3 had cerebellar dysfunction; 10 had neuropathy; 1 had a Babinski sign and none were entirely normal. In the normal folate group there were 8 alcoholics of whom 3 had an OBS; 1 had cerebellar dysfunction; 4 had neuropathy; none had a Babinski sign and 2 were entirely normal. Though the difference between these groups is not statistically significant at the 5% level, the frequency of all abnormal neurologic signs was considerably higher in the low folate group.

Non-alcoholic patients were then studied (Table 5). In the low folate group 9 out of 12 had an OBS; none had cerebellar dysfunction; 4 had neuropathy ; 4 demonstrated a Babinski sign and 2 had no abnormal findings. In the normal folate group 5 of 13 had an OBS; none had cerebellar dysfunction;

3 had neuropathy; none had a Babinski sign and 6 had no abnormal findings. The more frequent finding of a Babinski sign in the low folate group was statistically significant ($p < .025$), and the incidence of an OBS was much higher in this group also ($p < .07$).

The folate deficient patients were divided into alcoholic and non-alcoholic groups (Table 6). In the alcoholic group, 8 of 12 had an OBS; 3 had cerebellar dysfunction and 10 had neuropathy. In the 12 non-alcoholics, the incidence of OBS was similar to that in alcoholics but none had cerebellar dysfunction and only 4 had neuropathy. Two of the non-alcoholics were entirely normal while all the alcoholics had abnormal findings. Thus, the incidence of cerebellar dysfunction and neuropathy were significantly higher in the alcoholic group.

Finally, only those patients without any condition that is ordinarily associated with neurological signs were studied (Table 7). Excluded were patients with alcoholism, diabetes, renal disease, metastatic carcinoma, malnutrition and those over 80 years of age. In the low folate group, 4 of 5 had abnormal findings. In the normal folate group of 8 patients, one had an abnormal examination and 2 had only the finding of depression in the absence of other signs of intellectual impairment. If these 2 patients are not considered abnormal, the incidence of abnormal findings was significantly greater in the low folate group ($p < .014$).

DISCUSSION

The initial comparison of patients with a folic acid deficiency and those without such a deficiency shows a significant difference in the incidence of OBS and of a Babinski reflex. The finding of a neuropathy is much more common in those patients with a folic acid deficiency but not significantly so. The finding of cerebellar dysfunction is not markedly different in the two groups. This suggests that folate deficiency may lead to OBS, pyramidal tract damage and neuropathy. However, this association does not prove a causal relationship. Factors such as age, sex and other conditions must also be considered. In this study there was a close correlation in the age and sex of the two groups. The two most common associated conditions were anemia and alcoholism and it is clear that their role must be evaluated.

The patients with a folic acid deficiency were considerably more anemic than those in the normal folate control group. This was to be expected since folate deficiency is a known cause of megaloblastic anemia[6]. In an attempt to assess the role that might be played by anemia in the development of neurological signs, those patients with Hb $>$ 10 were divided into normal and folate deficient groups and compared (Table 2). Once again there was a statistically significant difference in the finding of a Babinski reflex in the low folate group (leading to the assumption that the low folate was a more critical determinant of this finding than anemia). OBS and neuropathy were twice as prevalent in the low folate group but this just fell short of statistical significance. Thus, it would appear that folate deficiency may be a critical determinant in the development of a neurological deficit.

To evaluate further the role played by anemia in the development of neurologic signs, the patients with folate deficiency were divided into those with Hb $\leq$ 10 and Hb $>$ 10 (Table 3). There were 12 in each group. If, as postulated earlier, low folate is a more critical determinant in the development of neurological deficits than is severe anemia, there should have been no

significant difference between the two groups. This hypothesis is indeed borne out. The finding of a Babinski reflex, which had been statistically significant when comparing a low folate group with a normal folate group (Tables 1 and 2), is nearly the same in the anemic and non-anemic groups of folate deficient patients. Similarly, OBS was seen in 9/12, 75% of the anemic group and 8/12, 66.7% of the non-anemic group. The incidence of neuropathy was 6/12 (50%) in the anemic folate deficient patients and 8/12 (66.7%) in the non-anemic ones. This very close correlation in the incidence of abnormalities between these two groups indicates that anemia per se is not a critical determinant of any of the neurological findings even though anemia is more prevalent in the folate deficient population.

It is clear that the role played by alcohol must be studied since alcoholism and folic acid deficiency frequently accompany each other. In this study 50% (12/24) of the low folate patients were alcoholics as were 38.4% (8/21) of the normal folate group.

The first comparison made is between alcoholics with folate deficiency and alcoholics with normal serum folate (Table 4). There was a greater incidence of all neurological deficits in the folate deficient group of alcoholics but the difference between the two groups did not turn out to be statistically significant at $p < .05$, probably because of the small size of the population studied. This trend gives further evidence supporting the role of folic acid deficiency in the development of these findings. However, it could be argued that folate deficient alcoholics were in worse general condition than alcoholics with normal folates.

To eliminate the role played by alcoholism as a factor in neurologic deterioration, non-alcoholic patients were grouped by folate level (Table 5). The Babinski sign was found significantly more frequently in the low folate group. This further supports the belief that folic acid deficiency is a key factor in the development of pyramidal damage. The finding of an OBS was

considerably higher in the low folate group (9/12) than the normal folate group (5/13) but the size of the sample supported this only at the 93% level of probability. The strong trend towards an increased incidence of OBS in the low folate group in an alcoholic population (Table 4) and the low folate group in a non-alcoholic population (Table 5) further supports the concept that folic acid deficiency is an important factor in the development of this finding. The incidence of neuropathy in non-alcoholics was low irrespective of folate level. It occurred in 4 of 12 with low folates and 3 of 13 with normal folates. However, neuropathy was quite common amongst alcoholics, folate deficient or not, though somewhat more so in the low folate group (83% vs. 50%). These results imply that the trend towards an increased incidence of neuropathy in a folate deficient population when compared to a normal folate population is more a function of alcoholism than of the folic acid deficiency alone. The importance of alcoholism in the development of cerebellar dysfunction is indicated by the absence of cerebellar findings in non-alcoholics, folate deficient or not.

Support for these conclusions is provided in Table 6 where the folate deficient alcoholics are compared with folate deficient non-alcoholics. There were 12 patients in each group. If the development of neurological abnormalities is determined primarily by folic acid deficiency then one would expect a close correlation between the incidence of neurologic signs in the two groups. The incidence of OBS was essentially the same in the two groups but there was considerably greater incidence of cerebellar dysfunction and neuropathy in alcoholic patients than non-alcoholic patients. The somewhat increased incidence of a Babinski reflex in the non-alcoholic patients with a low folate than the alcoholic patients with low folate is not significant. It is not inconsistent with the conclusion that folate deficiency may cause pyramidal tract dysfunction and that alcoholism is not a critical factor in the development of this finding.

As previously mentioned, the association between folate deficiency and certain neurological abnormalities does not prove a causal relationship. Other factors associated with low folate could cause neurological signs and some of these factors were examined in detail in this study. Certainly, the multiple nutritional deficiencies that may be seen in conjunction with folate deficiency must be considered. Vitamin B_{12} is one of these factors and in this study almost all patients had normal levels. In the low folate group, 18 of 20 patients who had serum vitamin B_{12} determinations had normal levels. One patient had a slightly depressed level and one had a very low level with a normal Schilling test. In the control group, all 17 patients who had vitamin B_{12} determinations had normal levels.

To eliminate as many potential etiologic factors as possible, a group of patients whose conditions are not usually associated with neurological abnormalities were compared with respect to folate levels (Table 7). If we exclude for the moment the isolated finding of depression in the absence of other evidence of organic mental impairment, only 1 of 8 patients with normal folate levels was abnormal; on the other hand, 4 of 5 folate deficient patients were abnormal. This difference is highly significant ($p < .014$). This lends further evidence to a fole for folate deficiency in the development of neurological findings but does not prove the point; for this would require evidence of remission of the neurological signs after treatment with folate alone.

In this study the abnormal sensory findings on neurological exam were categorized as neuropathy. The clinical picture was often a mixture of signs of the peripheral nerve and the spinal cord. Some of the signs may have been due to peripheral nerve involvement alone and some to involvement

of the spinal cord as well. This distinction is difficult to make and I chose to include all sensory impairment in the category of peripheral neuropathy. Thus, this study does not rule out a possible role of folic acid deficiency in the development of posterior column dysfunction.

In addition to this study, several other investigators have attempted to assess the role played by folic acid deficiency in the development of neuropsychiatric disease. These studies provided the background for this work.

a) Studies in Epileptic Patients

Reynolds (1970) has reviewed the evidence from studies of serum, red cell and CSF folate levels indicating that the three major drugs in the treatment of epilepsy (phenobarbital, diphenylhydantoin and primidone) may affect folate metabolism in the majority of epileptic patients. Reynolds et al (1966) suggested that drug induced folate deficiency may contribute to psychiatric and neurological complications in these patients. The following evidence supports this hypothesis:

1) Association of mental illness with low folate levels in serum, red cells and CSF -

Reynolds, Preece and Chanarin reported that serum folate levels were lower in epileptic patients with various abnormal mental states than in those with normal mental states, though this was statistically significant only in patients with dementia and schizophrenia-like psychoses.

Snaith, Mehta and Raby found epileptic patients with mental illness had significantly lower serum folate levels than epileptic patients without mental illness, although no particular type of psychiatric syndrome was

predominant.

Callaghan, Mitchell and Cotter found much lower serum folate levels in psychotic epileptic patients than in non-psychotic epileptics.

Preece, Reynolds and Johnson reported a significant lowering of serum and red cell folate in epileptic patients with psychiatric illness, as compared with controls and epileptic patients with normal mentat states.

Significantly lower CSF folate levels were found by Reynolds, Preece and Chanarin in epileptic patients with psychiatric illness than in epileptic patients with normal mental states.

2) Results of treatment

In a study of 26 chronic epileptic patients with folic acid deficiency due to anticonvulsant drugs, Reynolds (1967) noted that the mental state improved in 22 when treated with folic acid. The improvement took the form of increased drive and initiative, speed of cerebration, alertness, concentration, self-confidence and independence and sociability. Favorable changes in mood and behavior were also noted.

In a 1970 study Neubauer treated 50 folate deficient epileptic children with a combination of folic acid and vitamin B_{12}. Improvement in mental condition occurred from 5-8 weeks after beginning treatment in some of the younger children and it was recommended that both folic acid and vitamin B_{12} be given as soon as a patient is started on anticonvulsant drugs to prevent mental deterioration.

On the other hand, the following evidence has been offered against the hypothesis that folate deficiency contributes to psychiatric and neurological complications in epileptic patients:

Jensen and Olesen (1969) studied 34 patients suffering from epilepsy and treated with anticonvulsant drugs. Although 91% of these patients had subnormal serum folate levels, they reported that only one of these patients

had subnormal whole blood folate levels. They concluded that in spite of the subnormal serum folate levels, no folate deficiency state was found. These results are somewhat difficult to interpret because no controls were included.

Jensen and Olesen (1970) also did a double blind study in which 24 of their patients with subnormal serum folate were treated with folic acid. They evaluated the effect of the vitamin on the mental state, fit frequency, hematological condition and serum levels of diphenylhydantoin and phenobarbital. With the exception of a slight decrease in serum diphenylhydantoin levels no changes that could be ascribed to folic acid treatment could be found. They concluded that no objective evidence has been reported for a causal relationship between folate deficiency and neuropsychiatric disorders. These results are also subject to question since all the patients were demented and the course of treatment did not include vitamin B_{12}, the importance of which has been emphasized by both Reynolds and Neubauer.

Weckman and Lehtovaara also question any relationship between anticonvulsant drugs, folate metabolism and psychiatric illness, since they found no significant difference in CSF folate levels between treated epileptic, untreated epileptic and neurological control patients. However, they are the only authors who have not found lowering of serum folate values in epileptic patients and their control CSF values are much lower than in other studies.

Ralston, Snaith and Hinly confirmed reports that anticonvulsants lowered serum folate levels and probably deplete body stores of folic acid. In a double blind trial of folic acid for 3 months in long tern epileptic patients with serum folates less than 3 ng/ml no significant changes in behavior were found. However, they concluded that they hadn't yet repleted body stores of folic acid after the three months of therapy.

b) Studies in non-epileptic patients

In 1967, Carney measured serum folates on 423 psychiatric in-patients. He found that there were significantly more patients with values less than 2 ng/ml (low folate) than controls. The most striking associations with low serum folate were chronicity of illness, a history of medication and the predominance of certain diagnoses- namely epilepsy, endogenous depression and organic brain syndrome. He concluded that folate deficiency appeared common enough in the mentally ill to justify carrying out serum folate as a routine admission procedure and advised treatment with folic acid and vitamin B_{12} in patients with subnormal serum folate in the hope of attaining mental as well as physical improvement. In a follow-up study, low folate patients with endogenous depression, schizophrenia and organic psychoses who were treated with folic acid were discharged more quickly and were in a better clinical state at discharge than those who had not received folate. Low folate patients with other diagnoses failed to show these improvements when given the vitamin .

Grant, Hoffbrand and Wells examined 7 patients in a neurological hospital with megaloblastic hemopoiesis and folate deficiency. Three of them had a peripheral neuropathy and one of them and possibly a second had early spinal cord involvement. Marked subjective and some objective neurological improvement occurred with folic acid therapy. The remaining four patients had spastic paraplegias of unknown etiology and folic acid did not affect their neurological status. They did not find this surprising even if there was a link between the neurological disability and folate deficiency since once spinal cord disease is well established it is resistant to therapy.

Strachan and Henderson described two patients with megaloblastic anemia who also presented with advanced dementia. They were treated with folic acid and in addition to curing the anemia, a marked improvement in the mental state was noted in one and a complete return to normality was seen in the second.

Pincus, Reynolds, and Glaser have also presented a case of a woman with severe folate deficiency and clinical picture of megaloblastic anemia, dementia, impairment of posterior column functions, absent reflexes and bilateral Babinski signs. All these abnormalities resolved on folic acid therapy.

Ahmed has very recently reported a case of a woman with numbness in her feet and legs, marked weakness in the legs and absent vibratory and position sense in the legs. Romberg's sign was positive and Babinski's sign was present bilaterally. She had a hemoglobin of 8.2 and an MCV of 117 with a serum folate of 0.6 ng/ml. She was started on folate and physical improvement was reported as remarkable. Her legs became stronger, the numbness disappeared and no sensory loss was detected but the plantars remained upgoing.

Several patients with three separate inborn errors of folate metabolism have been studied by Arakawa. The clinical features he observed were mental retardation and abnormalities on electroencephalogram and pneumoencephalogram.

One of the important methodologic questions which can be raised about many studies of folate deficiency, including this one, relates to the adequacy of serum folic acid as an index of CNS folate levels. It is not clear how the serum level reflects the actual level in the CNS. Not all persons with folic acid deficiency as determined by serum values develop neurologic complications. There does not appear to be any exact correlation between the hematologic state and neurological disease. In this study 9 patients with markedly lowered serum folate levels had bone marrow examinations. Only 6 of these showed megaloblastic changes. If megaloblastosis was an index of the central folate stores, one would expect a high correlation with severe neurologic impairment. Yet, of the 6 with megaloblastic marrows, 2 had completely normal neurologic examinations, and 2 had evidence of OBS only. These observations are not surprising in light of what is known about vitamin B_{12} deficiency. Neurologic symptoms do not develop in all patients with pernicious anemia. For unknown

reasons, some patients develop subacute combined degeneration before the onset of anemia, while others show no evidence of neurologic disease, even after protracted and severe anemia.[9] Reynolds (1967) has suggested that genetic, anatomical, psychosocial, personality and other factors of an unknown nature may determine the form of response to a common biochemical stress to the nervous system. However complicated such factors may be, it also seems likely that serum folate and/or the associated hematologic changes of folate deficiency provide only a rough guide to the actual state of the central nervous system. Administration of folic acid, for example, raises serum but not necessarily CSF levels (Levitt, et al and B. Gallagher, unpublished data). It seems likely on the basis of all these studies that folic acid is important in normal neural functioning but many questions remain to be answered about the role of folic acid in the nervous system.

SUMMARY

Twenty-four patients with a folic acid deficiency were studied. These patients all had serum folate values less than 3 ng/ml. They were compared with normal folate controls which consisted of a group of 21 patients. These patients all had serum folate values greater than 6.9 ng/ml.

A comparison was made between the low folate group and the normal folate control group. In the low folate group 17/24 had an organic brain syndrome 3/24 had cerebellar dysfunction, 4/24 had a neuropathy and 5/24 demonstrated a Babinski sign. In the normal folate group 8/21 had an OBS, 1/21 had cerebellar dysfunction, 7/21 had a neuropathy and none had a Babinski sign. The difference between the two groups is statistically significant at $p < .03$ in the finding of an organic brain syndrome and a Babinski sign. The incidence of neuropathy was considerably higher in the low folate group. There was little difference in the two groups in the finding of cerebellar dysfunction.

The patients with a folic acid deficiency were considerably more anemic than the normal folate control group. Only 50% (12/24) of the folate deficient

patients had a Hb > 10 while 90.5% (19/21) of the normal folate group had a Hb > 10. Comparisons were made to determine the role played by anemia in the development of neurological or psychiatric disorders. It was determined that the anemia did not play a significant role.

In this study 50% (12/24) of the low folate patients were alcoholics and 38.4% (8/21) of the normal folate group were alcoholics. Comparisons were made to delineate the role played by alcohol in the development of neuropsychiatric problems in patients with folic acid deficiency. It was determined that the findings of organic brain syndrome, and of a Babinski sign were primarily on the basis of folate deficiency while the finding of a neuropathy was in large part due to alcoholism. Cerebellar dysfunction, although not a significant finding, is also largely a function of alcoholism.

It is clear that many questions remain to be answered about the role of folic acid in the nervous system and it is hoped that larger studies with long term follow-up will be done.

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Name	Sex	Age	Folate	B_{12}	Hb	Marrow	Diagnosis	Neuropsychiatric
O.A. 57-40-93	F	28	1.6	180	10.1	MEG	Alcoholism Heroin Addiction Malnutrition	Paresthesias Depression Apathy
H.D. 56-69-57	F	30	1.2	1470	10.0		Alcoholism Laennec's Cirrhosis Pneumonia	Sensorimotor Neuropathy Tremor
R.B. 25-59-60	M	33	1.3	980	7.6	Micro- angio- pathic"	Malnutrition Previous gastrec- temy (ulcers) Diabetes	Organic Brain Syndrome Depression Severe Neuropathy Mainly motor with marked prox wasting, absent reflexes, P↑↑
C.B. 73-15-92	M	31	2.2	1700	7.7	Erythroid Hyperplasia	Alcoholism Chronic Pancreatitis	Organic Brain Syndrome Cerebellar Disease Sens-Motor Neuropathy K+A J absent (+ wasting)
G.E. VA 247-24-12-95	M	47	2.6	330	5.8		Chronic Renal Disease	Depression and apathy
J.B. VA 012-12-08-38	M	50	2.7	440	12.8		Alcoholism Malnutrition Alc. Hepatitis	OBS Motor Neuropathy K+A J absent (+wasting)
E.W. 56-31-99	F	50	1.9	950	9.7	Erythroid Hyperplasia	Recurrent anemia Phlebitis	OBS Unexplained papilledema EEG negative
J.W. 23-67-05	M	50	1.2		12.4	MEG	Pneumonia	N1
T.M. VA 048-05-03-06	M	50	1.2	780	6.1	MEG	Laennec's Cirrhosis Alcoholism GI bleed (duo. ulcer) Diabetes	Myopathic weakness, wasting esp. proximal. Reflexes present, absent V.S.
L.M. VA 048-05-03-06	M	50	1.7 CSF 10.4	545	10.8		Ulcerative colitis	Sensory-motor neuropathy K & AJ absent VS ↓

Name	Sex	Age	Folate	B_{12}	Hb	Marrow	Diagnosis	Neuropsychiatric
B.J. VA 045-09-68-61	M	56	2.6	390	11.8		Alcoholism Malnutrition	Memory Impairment Tremor Sens-Motor Neuropathy (legs: pp ↓ PS ↓; AJ o)
T.D. VA 049-07-60-54	M	58	2.5	860	11.5		Diabetes Laennec's Cirrhosis (biopsy) Diverticulosis CHF	Sens-Motor Neuropathy in legs (pp, VS ↓ AJ o)
E.S. S3-69-88	M	64	1	1350	10.9		Alcoholism G.I. Bleed	Organic Brain Syndrome Seizures in past (withdrawal?) pp ↑↑
E.C. 32-89-78	M	65	1	240	8.7	MEG	Alcoholism Malnutrition Pneumonia	Organic Brain Syndrome Absent AJ (+ paresthesias)
C.W. 23-27-48	F	66	1.9	640	7.5		Anemia Poor Diet Submandibular tumor	Organic Brain Syndrome
T.A. VA 251-10-97-79	M	51	1		9.6	MEG	Alcoholism Previous Gastrectomy (ulcer) Heart failure Cellulitis	Organic Brain Syndrome
G.O. 78-68-01	F	70	1.6	270	11.9		Ca Breast Pneumonia	Organic Brain Syndrome Neuropathy K & AJ absent pp ↓ legs P ↑↑ Paresthesia

Name	Sex	Age	Folate	B_{12}	Hb	Marrow	Diagnosis	Neuropsychiatric
B.M. 68-63-70	M	71	1.6		10.0		Ca Prostate Laparotomy	Organic Brain Syndrome Neuropathy, K & AJ absent V.S.↓ legs. Distal weakness wasting hands
W.N. 78-35-72	M	73	1.3	1700	11.0		Alcoholism Laennec's Cirrhosis	Organic Brain Syndrome Absent V.S. Legs
J.C. 55-29-65	M	77	1.8	440	11.9		Pulmonary Disease	Unexplained P↑↑
F.R. 66-68-41	M	81	1	1700	6		Malnutrition Scurvy	Organic Brain Syndrome P ↑↑
M.V. 07-02-54	M	94	1.2		11.5		Pulmonary Disease	Organic Brain Syndrome Depression
P.W. 78-98-33	F	37	1	50*	5.3	MEG	Malnutrition	N1
D.B. 79-89-10	M	51	2.4	1100	12.1		Laennec's Cirrhosis (biopsy)	K & AJ absent

K & AJ = knee and ankle jerk
P = plantar reflex (Babinski)
PS = position sense
VS = vibratory sense
pp = pinprick

*Patient had a normal Schilling test

Name	Sex	Age	Folate	B_{12}	Hb	Marrow	Diagnosis	Neuropsychiatric
E.A. 79-77-92	M	63	13		11.8		Laennec's Cirrhosis Alcoholism	Depression K & AJ absent; pp & VS ↓
J.C. 10-17-85	M	61	7.8	1100	12.5		Laennec's Cirrhosis Diabetes Alcoholism	Organic Brain Syndrome AJ absent; pp & VS ↓
A.D. 73-59-87	F	56	8.8	3600	10.7		Diabetes (ketoacidosis)	Nl
R.H. 61-10-16	F	70	22.8	850	16.5		Anemia (Fe Def.)	Depression
M.H. 79-43-12	F	50	14	360	13.1		Malabsorption	AJ absent
H.J. 49-82-83	M	30	7.6		10.6		Laennec's Cirrhosis UGI bleed (ulcer)	Nl
E.M. 79-77-72	M	56	7.4		12.7		Malabsorption Sm. Bowel Disease	Depression and Apathy
E.N. 13-39-16	F	67	10	340	13.9		Amebic Dysentery	Nl
A.P. 09-31-38	M	52	11	1200	10.2	Normo- cellular	Ca Pancreas	Nl
W.P. 04-45-15	M	81	13	580	11.6		Pneumonia Diverticulosis ? Ca colon	Organic Brain Syndrome

Name	Sex	Age	Folate	B_{12}	Hb	Marrow	Diagnosis	Neuropsychiatric
J.T. 13-97-92	M	71	17	440	10.8	Normo-cellular	ASHD (pul. Edema) Diabetes Chronic Renal Disease (secondary to diabetes)	K & AJ absent pp & VS ↓
V.T. 78-79-04	F	54	25	1450	13.8	Hypo-cellular	Laennec's Cirrhosis (biopsy) Diabetes Thrombocytopenia	Nl
W.W. 80-60-65	M	55	15.5	320	6.5		UGI bleed (duo. ulcer)	Nl
S.G. VA 043-16-20-26	M	50	25		15.9		Alcoholism CHF	AJ absent
E.M. VA 044-32-42-61	M	30	10.8	200	11.3		Anemia	Nl
D.H. VA 044-14-09-34	M	47	6.9	940	12.8		Laennec's Cirrhosis (biopsy). Previous Gastrectomy for Duo. ulcer	AJ absent VS ↓
A.C. 81-11-25	M	71	16.8	1020	13.2		Alcoholism GI bleed	Memory ↓
J.R. VA 043-01-86-49	M	53	725	640	11.6		Alcoholism Laennec's Cirrhosis	Tremor
H.R.	M	56	10.4	570	17.7		Pul. Disease	Nl

CONTROLS (cont.)

Name	Sex	Age	Folate	B_{12}	Hb	Marrow	Diagnosis	Neuropsychiatric
G.L. 06-65-33	F	76	8.6	760	13.0		Ca Breast Previous Colon resection for obstruction 2^{o} diverticula	Organic Brain Syndrome
L.W. 79-55-48	M	44	7.6	450	9.1		Chronic Glomerulo-nephritis	Organic Brain Syndrome K & AJ absent

TABLE 1: Comparison of Findings in Low Folate vs. Normal Folate Control Group

Finding	Low Folate	Normal Folate	Statistical Significance
OBS*	17/24 70.8%	8/21 39.0%	$\chi^2 = 4.96$ $p < .03$
Cerebellar Dysfunction	3/24 12.5%	1/21 4.8%	N. S.**
Neuropathy	14/24 58.3%	7/21 33.3%	$\chi^2 = 2.813$ $p < .10$
Babinski	5/24 20.8%	0/21 0%	$\chi^2 = 4.79$ $p < .03$

*OBS = Organic Brain Syndrome
**N.S. = Not significant

TABLE 2: Comparison of Findings in Patients with Hb > 10 and Low Folate vs. Hb > 10 and Normal Folate

Finding	Low Folate	Normal Folate	Statistical Significance
OBS	8/12 66.7%	7/19 36.8%	$\chi^2 = 2.99$ $p < .09$
Cerebellar Dysfunction	1/12 8.3%	1/19 5.3%	N.S.
Neuropathy	8/12 66.7%	6/19 31.6%	$\chi^2 = 3.71$ $p < .06$
Babinski	3/12 25%	0/19 0	$\chi^2 = 5.0$ $p = .025$

TABLE 3: Comparison of findings in patients with Hb $\leq$ 10 and low folate vs. Hb $>$ 10 and low folate.

Finding	Hb $\leq$ 10	Hb $>$ 10	Statistical Significance
OBS	9/12 (75%)	8/12 (66.7%)	N.S.
Cerebellar Dysfunction	2/12 (6.7%)	1/12 (8.3%)	N.S.
Neuropathy	6/12 (50%)	8/12 (66.7%)	N.S.
Babinski	2/12 (16.7%)	3/12 (25%)	N.S.

TABLE 4: Comparison of findings in alcoholic patients with low folate vs. alcoholic with normal folate.

Finding	Low Folate	Normal Folate	Statistical Significance
OBS and Psychiatric Disorders	8/12 (66.7%)	3/8 (37.5%)	N.S.
Cerebellar Dysfunction	3/12 (25%)	1/8 (12.5%)	N.S.
Neuropathy	10/12 (83.3%)	4/8 (50%)	N.S.
Babinski	1/12 8.3%	0/18 (0%)	N.S.

TABLE 5: Comparison of findings in non-alcoholic patients with low folate vs. non-alcoholics with normal folate

Finding	Low Folate	Normal Folate	Statistical Significance
OBS and Psychiatric Disorders	9/12 (75%)	5/13 (38.5%)	$\chi^2 = 3.45$ $p < .07$
Cerebellar Dysfunction	0/12 (0%)	0/13 (0%)	N.S.
Neuropathy	4/12 (33.3%)	3/13 (23.1%)	N.S.
Babinski	4/12 (33.3%)	0/13 (0%)	$\chi^2 = 5.26$ $p < .025$

TABLE 6: Comparison of Findings in alcoholic patients with low folate vs non-alcoholics with low folate

Finding	Alcoholic	Non-alcoholic	Statistical Significance
OBS and Psychiatric Disorders	8/12 (66.7%)	9/12 (75%)	N.S.
Cerebellar Dysfunction	3/12 (25%)	0/12 (0%)	$\chi^2 = 3.42$ $p < .07$
Neuropathy	10/12 (83.3%)	4/12 (33.3%)	$\chi^2 = 6.18$ $p < .014$
Babinski	1/12 (8.3%)	4/12 (33.3%)	N.S.

TABLE 7: Comparison of Patients with Diseases not Usually Associated with Neurologic Signs

LOW FOLATE

Diagnosis	Age	B_{12}	Findings
Pneumonia	50	440	N1
Phlebitis	50	950	OBS
Ulcerative Colitis	50	545	Neuropathy
Cancer Prostate (non-metastatic)	71	-	Neuropathy OBS
Pul. Dis.	77	440	Babinski
	Avg. 59.6		

NORMAL FOLATE

Diagnosis	Age	B_{12}	Findings
Fe Deficiency	70	850	Depression
Malabsorption	50	360	Neuropathy
Malabsorption	56	-	Depression
Amebic Dyssentery	67	340	N1
Cancer Pancreas	52	1200	N1
Ulcer	55	320	N1
Anemia	30	200	N1
Pul. Dis.	56	570	N1
	Avg. 54.5		

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